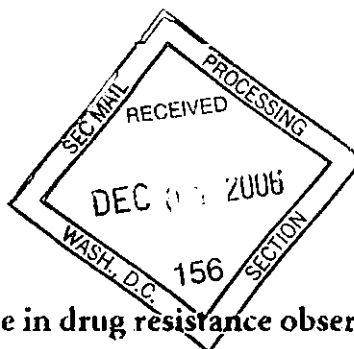




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Update on Tamiflu: no increase in drug resistance observed

Incidence of resistance rates remain low in treated patients (0.32% adults, 4.1% children)

With the public interest in Tamiflu continuing, Roche keeps interested physicians and governments updated on current developments and today, informs on the topic of resistance. There have been no new cases of resistance seen in patients infected with H5N1 virus ('bird flu') since March 2005 and scientific data does not substantiate increased resistance to Tamiflu (oseltamivir). Roche is providing this update on the topic so that physicians and governments can be confident that Tamiflu can continue to be effectively used in the treatment and prophylaxis of seasonal and H5N1 influenza.

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"Over the last few months, there has been erroneous speculation that resistance to Tamiflu is increasing. This is an area that Roche and independent groups have been closely monitoring and there is no scientific evidence to suggest this is happening", said David Reddy, Roche's Influenza Pandemic Taskforce Leader. "Governments can be confident that Tamiflu remains a critical drug, as recommended by the WHO, for stockpiling to prepare for an influenza pandemic and for physicians and patients to treat and prevent flu when it hits".

All H5N1 viruses that have been tested are susceptible to neuraminidase inhibitors like Tamiflu as described recently in the New England Journal of Medicine¹.

Resistance not on the increase

As with any antiviral medication, there is a theoretical risk that a virus may emerge with decreased sensitivity to a drug. Roche monitors for any emerging resistance to Tamiflu both internally and externally via bodies such as the Neuraminidase Inhibitor Susceptibility Network, (NISN). The data, collected from thousands of patients worldwide who were treated with Tamiflu for seasonal influenza, generally indicate that the incidence of resistant viruses is rare (0.32% in adults and 4.1% in children). The higher incidence of resistant virus among children compared with adults

appears to be related to higher levels of virus and longer duration of viral shedding. One small study in children in Japan did report a higher rate of resistance³, however, in this study children received a different and often lower dosing schedule relative to the dosing used in children the West and some were dosed for less than the recommended 5 days. Surveillance during clinical use in Japan, where Tamiflu has been prescribed most often so far - 45 million patients have been treated with the antiviral - has shown that the low rates of resistance seen to date are not increasing. Of the few Tamiflu-resistant viruses so far identified, most cause less severe infections and are less capable of transmission.

Resistance to H5N1 avian virus

The possible development of anti-viral resistance is of concern for pandemic planning and preparedness. However, to date, there have only been three documented cases of Tamiflu resistance to avian influenza H5N1.^{4,5} In one case, the prophylactic dose (75 mg daily) rather than the treatment dose (75 mg twice daily) was given to a patient already exhibiting clinical symptoms, thus under-dosing the patient and increasing the risk of resistance.⁴ Once the twice daily treatment dose was provided, the patient recovered from their illness. Again this resistant virus was shown to cause less severe infection and was less capable of transmission. In the other two cases, the recommended dose and duration of oseltamivir was followed.⁵ However, while one patient received treatment on the second day of illness, the other patient started treatment on the sixth day of illness. No further cases of resistance of H5N1 to Tamiflu have been identified or reported since March 2005, despite the number of infected patients increasing. A recent study has also shown that the responsiveness of H5N1 viruses isolated in 2004 and 2005 to oseltamivir is about 10-fold higher than of H5N1 virus isolated in 1997 and of currently circulating seasonal (H1N1) viruses⁶. This suggests that the virus has become more responsive to Tamiflu over time.

About influenza

Influenza, commonly called the 'flu', is a serious disease and annual outbreaks and epidemics are caused by influenza A and B viruses. Influenza is a highly contagious viral illness and is characterised by a sudden onset of debilitating clinical symptoms which affect the entire body. Up to 500 million people are infected by influenza and up to 500,000 deaths are attributed to influenza each year. Influenza complications occur in all patient groups and include bronchitis, sinusitis, otitis media, and pneumonia.

About Tamiflu

Tamiflu is designed to be active against all clinically relevant influenza A and B viruses and works by blocking the action of the neuraminidase (NAI) enzyme on the surface of the virus. When

neuraminidase is inhibited, the virus is not able to spread to and infect other cells in the body. It is licensed for the treatment and prophylaxis of influenza in children aged one year and above and in adults.

Roche's efforts to support government pandemic stockpiling

The World Health Organization (WHO) advises that stockpiling antivirals in advance is presently the only way to ensure that sufficient supplies are available in the event of a pandemic. Roche has been working closely with WHO and national governments to ensure governments are aware of the importance of stockpiling antivirals in the event of a pandemic situation. Roche has received and fulfilled pandemic orders for Tamiflu from more than 75 countries worldwide. The magnitude of these orders varies with some countries, France, Finland, Iceland, Ireland, Luxembourg, Netherlands, New Zealand, Norway, Switzerland and UK stockpiling or intending to stockpile adequate Tamiflu to cover 20-40% of their population. Roche has also donated 5.125 million courses of Tamiflu treatment to the WHO for international rapid response and regional response to a pandemic influenza strain.

Roche and Gilead

Tamiflu was invented by Gilead Sciences and licensed to Roche in 1996. Roche and Gilead partnered on clinical development, with Roche leading efforts to produce, register and bring the product to the markets. Under the terms of the companies' agreement, amended in November 2005, Gilead participates with Roche in the consideration of sub-licenses for the pandemic supply of oseltamivir. To ensure broader access to Tamiflu for all patients in need, Gilead has agreed to waive its right to full royalty payments for product sold under these sub-licenses.

About Roche

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. As a supplier of innovative products and services for the early detection, prevention, diagnosis and treatment of disease, the Group contributes on a broad range of fronts to improving people's health and quality of life. Roche is a world leader in diagnostics, the leading supplier of medicines for cancer and transplantation and a market leader in virology. In 2005 sales by the Pharmaceuticals Division totalled 27.3 billion Swiss francs, and the Diagnostics Division posted sales of 8.2 billion Swiss francs. Roche employs roughly 70,000 people in 150 countries and has R&D agreements and strategic alliances with numerous partners, including majority ownership interests in Genentech and Chugai. Additional information about the Roche Group is available on the Internet (www.roche.com).

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Additional information

- Roche Health Kiosk, Influenza
- About Tamiflu
- About influenza
- WHO: Global influenza programme
- WHO: Avian flu

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